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Wickstrom, J. -E.

2017-05

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Wickstrom , J -E , Laivuori , M , Aro , E , Sund , R T , Hautero , O , Venermo , M , Jalkanen , J & Hakovirta , H 2017 , ' Toe Pressure and Toe Brachial Index are Predictive of Cardiovascular Mortality, Overall Mortality, and Amputation Free Survival in Patients with Peripheral Artery Disease ' , European Journal of Vascular and Endovascular Surgery , vol. 53 , no. 5 , pp. 696-703 . <https://doi.org/10.1016/j.ejvs.2017.02.012>

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<http://hdl.handle.net/10138/236975>

<https://doi.org/10.1016/j.ejvs.2017.02.012>

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# Toe Pressure and Toe Brachial Index are Predictive of Cardiovascular Mortality, Overall Mortality, and Amputation Free Survival in Patients with Peripheral Artery Disease

J.-E. Wickström<sup>a</sup>, M. Laivuori<sup>b</sup>, E. Aro<sup>a</sup>, R.T. Sund<sup>c</sup>, O. Hautero<sup>a</sup>, M. Venermo<sup>b</sup>, J. Jalkanen<sup>a</sup>, H. Hakovirta<sup>a,\*</sup>

<sup>a</sup> Department of Vascular Surgery, Turku University Hospital and University of Turku, Turku, Finland

<sup>b</sup> Department of Vascular Surgery, University Hospital of Helsinki, Helsinki, Finland

<sup>c</sup> Centre for Research Methods, Department of Social Research, University of Helsinki, Helsinki, Finland

## WHAT THIS PAPER ADDS

In many vascular units, ankle pressure, ankle brachial pressure, toe pressure (TP), and toe brachial index (TBI) are essential measurements for clinical decision making and are routinely analysed in everyday practice. There are no earlier studies comparing all four variables and patient outcome in a single study setting. Based on the present observations it is suggested that non-invasive measurement of TP and TBI are associated with cardiovascular and overall mortality, as well as amputation free survival of patients with peripheral artery disease.

**Objective/Background:** Peripheral haemodynamic parameters are used to assess the presence and severity of peripheral artery disease (PAD). The prognostic value of ankle brachial index (ABI) has been thoroughly delineated. Nonetheless, the relative usefulness of ankle pressure (AP), ABI, toe pressure (TP), and toe brachial index (TBI) in assessing patient outcome has not been investigated in a concurrent study setting. This study aimed to resolve the association of all four non-invasive haemodynamic parameters in clinically symptomatic patients with PAD with cardiovascular mortality, overall mortality, and amputation free survival (AFS).

**Methods:** In total, 732 symptomatic patients with PAD admitted to the Department of Vascular Surgery for conventional angiography at Turku University Hospital, Turku, Finland, between January 2009 and August 2011 were reviewed retrospectively. Demographic factors, cardiovascular mortality, all-cause mortality, and above foot level amputations were obtained and assessed in relation to AP, ABI, TP, and TBI by means of Kaplan–Meier life tables and a multivariate Cox regression model.

**Results:** The haemodynamic parameter that was associated with poor 36 month general outcome was TP < 30 mmHg. Univariate Cox regression analysis of stratified values showed that TP and TBI associated significantly with mortality. In multivariate analysis both TP and TBI were associated with a significant risk of death. For TP < 30 mmHg and TBI < 0.25 the risk of cardiovascular mortality was hazard ratio [HR] 2.84, 95% confidence interval [CI] 1.75–4.61 [ $p < .001$ ]; HR 3.68, 95% CI 1.48–9.19 [ $p = .050$ ], respectively; all-cause mortality (HR 2.05, 95% CI 1.44–2.92 [ $p < .001$ ]; HR 2.53, 95% CI 1.35–4.74 [ $p = .040$ ], respectively); and amputation or death (HR 2.13, 95% CI 1.52–2.98 [ $p < .001$ ]; HR 2.46, 95% CI 1.38–4.40 [ $p = .050$ ], respectively)...

**Conclusion:** Among non-invasive haemodynamic measurements and pressure indices both TP and TBI appear to be associated with cardiovascular and overall mortality and AFS for patients with PAD presenting symptoms of the disease.

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Article history: Received 21 September 2016, Accepted 9 February 2017, Available online 11 March 2017

**Keywords:** ABI, Amputation free survival, Ankle pressure, Mortality, TBI, Toe pressure

## INTRODUCTION

Lower limb peripheral arterial disease (PAD) and, in particular, critical limb ischaemia (CLI) markedly increase the risk of both debilitating limb loss and adverse

cardiovascular events. Today, an estimated 200 million people worldwide are affected by PAD, with the number constantly increasing, owing not only to longer life expectancy, but also to manifestation of the disease at a younger age.<sup>1–3</sup> Early detection of PAD and initiation of optimal medical and conservative treatment is thus becoming increasingly important.

Measurements of ankle and toe systolic pressures (AP and TP, respectively) and their relation to that in the arm (ankle brachial index [ABI] and toe brachial index [TBI]) have

\* Corresponding author. Turku University Hospital, TE5 Hämeentie 11, 20521 Turku, Finland.

E-mail address: [haheha@utu.fi](mailto:haheha@utu.fi) (H. Hakovirta).

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<http://dx.doi.org/10.1016/j.ejvs.2017.02.012>

been widely applied to the initial assessment of peripheral circulation. The diagnostic limitations of ABI have been thoroughly addressed. Decreased ABI ( $< 0.9$ ) has been shown to be strongly associated with increased risk of myocardial infarction and cardiovascular death.<sup>4,5</sup> However, the usefulness of ABI may be reduced in conditions such as diabetes, chronic kidney disease, and advanced age, owing to arterial stiffening and incompressibility of the leg arteries at ankle level.<sup>6–8</sup> Both low and high ABI among diabetic patients correlate with increased risk of cardiovascular mortality in a U-shaped fashion.<sup>8,9</sup> Thus, arterial stiffening may reduce both the diagnostic and prognostic value of ABI, especially among diabetics.

As digital arteries are generally regarded as less susceptible to vessel stiffness, the use of TP and TBI has been recommended in order to overcome the influence of arterial incompressibility.<sup>6,9</sup> However, among diabetics the diagnostic value of TBI has been questioned.<sup>10,11</sup> The correlation of low TP with increased mortality and decreased amputation free survival (AFS) has been demonstrated in patients with incompressible leg arteries.<sup>12,13</sup>

In addition to AP and ABI, TP is used in the widely accepted TransAtlantic Inter-Society Consensus II (TASC II) classification of limb ischaemia.<sup>14–17</sup> Low TP appears to serve as a prognostic marker for wound healing in PAD.<sup>14</sup> Further risk stratification of patients with CLI based on the severity of tissue loss, ischaemia, and foot infection (Wifl) has recently been created by the Society for Vascular Surgery Lower Extremity Guidelines Committee.<sup>18</sup> Yet, not every patient with haemodynamic criteria for severe ischaemia, even according to Wifl, may require revascularisation.<sup>13</sup>

Even today, data regarding means of identifying which patients with PAD have the greatest risk of major cardiovascular events or amputation is limited. Non-invasive measurement of haemodynamic parameters is feasible and routinely carried out in vascular practice. However, the overall relative prognostic value of AP, ABI, TP, and TBI remains to be further elucidated. We have analysed the relationship between these parameters and mid-term cardiovascular and all-cause mortality, as well as AFS in vascular surgical patients. To the authors' knowledge, there are few previous data comparing all four parameters in a setting that encompasses all symptomatic patients with PAD.

## METHODS

### Study cohort

This retrospective study consisted of all consecutive symptomatic patients with PAD admitted to the Department of Vascular Surgery, Turku University Hospital, Turku, Finland, for either diagnostic or therapeutic conventional lower limb angiography (digital subtraction angiography [DSA]) from 1 June 2009 to 31 August 2011. The aim was to analyse the influence of peripheral pressures and pressure indices on 36 month survival at the time of clinical presentation with insufficient arterial circulation,

before any revascularisation procedures. Although 887 patients were recruited, standardised peripheral pressure measurements were available for only 732 patients. This is a result of poor availability of vascular laboratory measurements outside office hours. Patients were included irrespective of their earlier PAD history. The study protocol was approved by the local ethical committee of the Hospital District of South-West Finland. Owing to the retrospective nature of this study, informed patient consent was not required.

### Vascular laboratory

Standardised non-invasive haemodynamic measurements were carried out by experienced vascular technicians at Turku University Hospital Vascular Laboratory. Measurements were obtained with patients in a supine position with feet at heart level, using a Nicolet VasoGuard (Nicolet Vascular Inc. Madison, WI, USA) photoplethysmography (PPG) device in all patients. When stable signals were obtained, brachial, ankle, and digital cuffs were inflated until disappearance of the PPG signal, typically up to 200 mmHg. Brachial pressure, AP, and TP were determined by gradual deflation of the cuffs to the moment of reappearance of a pulsatile signal. Signals were later checked offline. TP was preferentially measured from the great toe or, if it was missing, from the nearest available toe. A mean of 3–5 measurements of TP was used for analysis. Either APs or TPs were available for 732 patients prior to possible revascularisation. AP and ABI were available for 720 patients, and TP and TBI for 717 patients. In 708 patients both measurements were available. Measurements for the clinically relevant limb were registered. When both limbs were symptomatic, measurements for the limb with the lowest TP were registered. Where TP was not available, measurements for the limb with the lowest AP were registered.

TP and TBI were not measurable in 15 patients with previous forefoot amputations or severe tissue loss involving the toes. AP was unavailable for 12 patients, either owing to pain or reduced ability to cooperate. Pressure indices for one patient were not available owing to apparently incompressible arteries in both upper extremities with bilateral non-occluded cuff pressures of  $> 250$  mmHg in the arms.

### Data collection

Patient baseline characteristics at admission, which served as the index date for follow-up, were retrospectively collected from the hospital electronic database. Only International Classification of Diseases (ICD) 10 coded diagnoses were registered. The following risk factors were collected for analysis: coronary artery disease (CAD), cerebrovascular disease (CVD), hypertension, active smoking, diabetes, sleep apnea, chronic obstructive pulmonary disease (COPD), end stage renal disease (ESRD), dyslipidemia, AP, ABI, TP, TBI, and serum creatinine level. Baseline medication including statins, clopidogrel, aspirin, warfarin, and

novel anticoagulants was registered from within electronic patient files where reliably available. A reliable medication history was unavailable for 51 patients (7.0%). Deaths within the patient cohort were registered for the first 36 months, which was the cutoff point for follow-up. Later, in 2015, the causes of death were collected from the Finnish centre for statistics, which has a 2 year delay in publishing official mortality data. For the purposes of this study, causes of death were categorized into cardiovascular and other. Only major (above- ankle) amputations were registered.

For statistical analysis, peripheral pressures were pooled into categories adapted from the TASC II recommendation.<sup>16</sup> Categories for ankle pressures were < 50 mmHg, 50–69 mmHg, and ≥ 70 mmHg, and indisputably incompressible leg arteries with a pressure of > 250 mmHg were assigned to category 4. TP data were pooled into three categories: 0–

29 mmHg, 30–49 mmHg, and ≥ 50 mmHg. Categories for ABI were chosen in accordance with their relationship to cardiovascular events, as presented by Mehler *et al.* as follows:<sup>19</sup> < 0.25, 0.25–0.49, 0.50–0.74, 0.75–0.89, 0.90–1.30, and > 1.30. Categories for TBI were as follows: < 0.25, 0.25–0.49, and ≥ 0.5. Cardiovascular deaths were collected according to the Finnish centre for statistics' classification. All cardiovascular causes of death were included namely ICD-10 diagnoses I00–I42.5 and I42.7–I99

### Statistical analyses

All statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY, USA). Group specific baseline characteristics are presented as percentages, and continuous variables as mean ± SD. Group variables were compared using Pearson's chi-square test. For continuous variables a Shapiro–Wilk test was run to test the normality of the variables. Variables were then compared by analysis of variance, as the continuous variables in each group were normally distributed.

Kaplan–Meier survival curves representing cumulative survival were constructed for the study groups based on haemodynamic measurements as described above. Survival curves for each variable in defined groups were compared using Wilcoxon statistics. For Cox regression analysis, a univariate analysis using the Cox model was first performed, then the variables with a *p* value < .15 in the univariate analysis were added to the model. All study outcomes—cardiovascular and overall mortality and AF—were analysed separately. For multivariate Cox regression analysis, haemodynamic measures resulting in *p* values < .15 on all outcomes, cardiovascular, and overall mortality and AFS were included. The highest group was selected as reference for categorical pressures and indices. To avoid false positive observations the *p* values were Bonferroni adjusted if they include multiple exposures. A *p* value < .05 was considered statistically significant.

**Table 1.** Demographic data from the study cohort.

Cohort demographics	Prevalence ( <i>n</i> = 732)
Mean ± SD age (y)	72 (11)
Sex (female)	42
CAD	43
CVD	17
Hypertension	70
Diabetes	41
Sleep apnoea	6
ESRD	10
Dyslipidemia	37
Smoking history	29
COPD	12
Antithrombotic	70
Anticoagulants	22
Statins	57

*Note.* Data are % unless otherwise indicated. CAD = coronary artery disease; CVD = cerebrovascular disease; ESRD = end stage renal disease; COPD = chronic obstructive pulmonary disease.

**Table 2.** Demographic data by defined toe pressure (TP) categories.

Cohort demographics	< 30 mmHg ( <i>n</i> = 232)	30–49 mmHg ( <i>n</i> = 227)	≥ 50 mmHg ( <i>n</i> = 258)	<i>p</i>
Mean ± SD age (y)	75 (11)	72 (11)	69 (9.6)	< .001
Sex (female)	41	42	41	.997
CAD	43	44	43	.898
CVD	16	15	19	.416
Hypertension	70	69	70	.891
Diabetes	43	43	37	.327
Sleep apnoea	3,4	8	7	.116
ESRD	8	13	8	.106
Dyslipidemia	34	35	42	.117
Smoking history	24	31	33	.087
COPD	13	10	15	.305
Antithrombotic	74	75	67	.947
Anticoagulant	24	22	24	.920
Statin	54	60	67%	.021

*Note.* Data are % unless otherwise indicated. An even distribution of most risk factors was detected. The prevalence of smoking history was significantly low in TP category < 30 mmHg, and the use of statins was significantly more common in higher TP categories. Statistical significance was tested using a chi-square test for categorical variables and *t* test for continuous variables. CAD = coronary artery disease; CVD = cerebrovascular disease; ESRD = end stage renal disease; COPD = chronic obstructive pulmonary disease.

## RESULTS

### Patient characteristics, pressure indices, and peripheral pressure categories

Forty-two percent of the study population were women and the mean age was  $72 \pm 11$  years. General patient characteristics are presented in Table 1. Category specific patient characteristics are shown in Table S1 for AP and Table S2 for TP (see Supplementary Material) (see Table 2).

### TP and patient outcome

The cardiovascular survival within TP groups was as follows: (i) TP < 30 mmHg: 29.4 months (SE 0.85; 95% confidence interval [CI] 27.7–31.0); (ii) TP 30–49 mmHg: 32.8 months (SE 0.67; 95% CI 31.5–34.1); (iii) TP  $\geq$  50 mmHg: 34.9 months (SE 0.45; 95% CI 34.1–35.8). Cardiovascular mortality was significantly increased in the group of patients with TP 0–29 mmHg compared with TP 30–49 mmHg ( $p = .001$ ) and TP  $\geq$  50 mmHg ( $p < .001$ ) (Fig. 1A). For overall survival (OS) and AFS, Kaplan–Meier curves are presented in Figs 2(A) and 3(A), respectively.

### AP and patient outcome

The cardiovascular survival within AP groups was as follows: (i) AP < 50 mmHg: 28.7 months (SE 1.5; 95% CI 25.8–31.7);

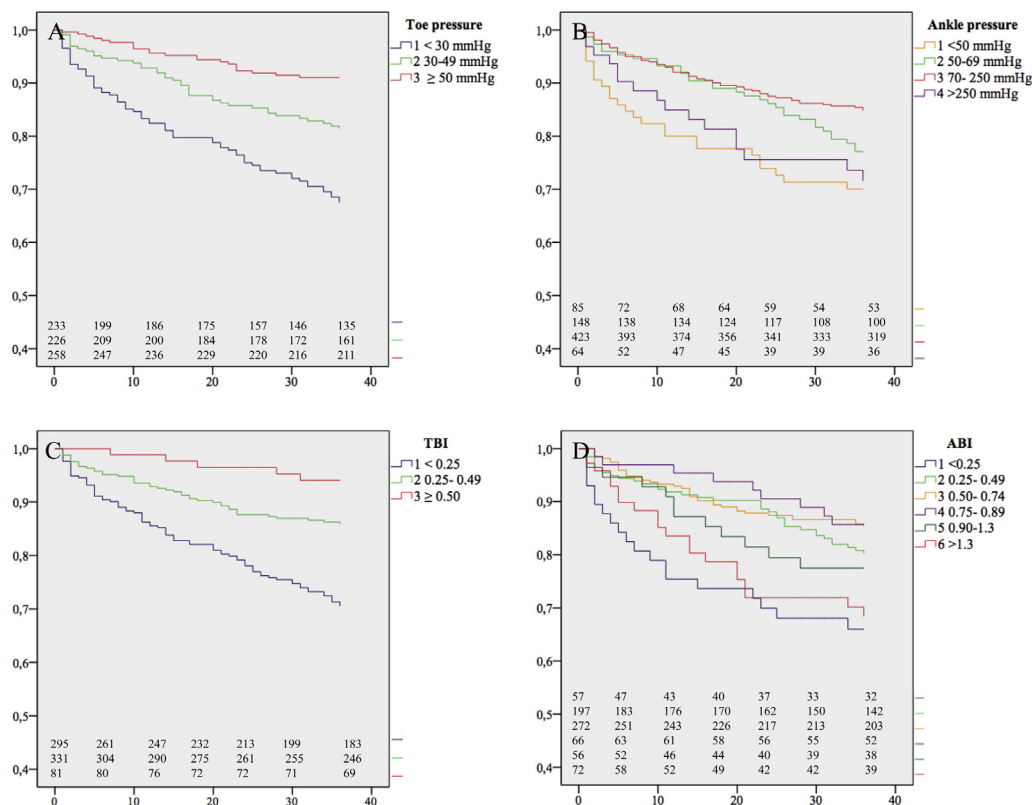
(ii) TP 50–69 mmHg: 32.6 months (SE 0.81; 95% CI 31.0–34.2); (iii) TP  $\geq$  70–250 mmHg: 33.4 months (SE 0.45; 95% CI 32.5–34.3); and (iv)  $>$  250 mmHg 30.2 months (SE 1.6; 95% CI 27.0–33.3). Patients with AP  $\geq$  70 mmHg had significantly less cardiovascular mortality than those with an AP < 50 mmHg ( $p < .001$ ) or incompressible leg arteries with an AP > 250 mmHg ( $p < .015$ ) (Fig. 1B). Corresponding Kaplan–Meier curves for OS and AFS are presented in Figs 2(B) and 3(B), respectively.

### TBI and patient outcome

Cardiovascular survival within the TBI groups was as follows: (i) TBI < 0.25: 30.3 months (SE 0.71; 95% CI 28.9–31.7); (ii) TBI 0.25–0.49: 33.5 months (SE 0.52; 95% CI 32.5–34.6); and (iii) TBI  $\geq$  0.50: 35.9 months (SE 0.52; 95% CI 34.9–36.9). Cardiovascular mortality in the group with a TBI < 0.25 was significantly increased compared with other groups (TBI 0.25–0.49:  $p < .001$ ; TBI  $\geq$  0.50:  $p < .001$  [Fig. 1C]). Kaplan–Meier curves for OS and AFS are presented in Figs 2(C) and 3(C), respectively.

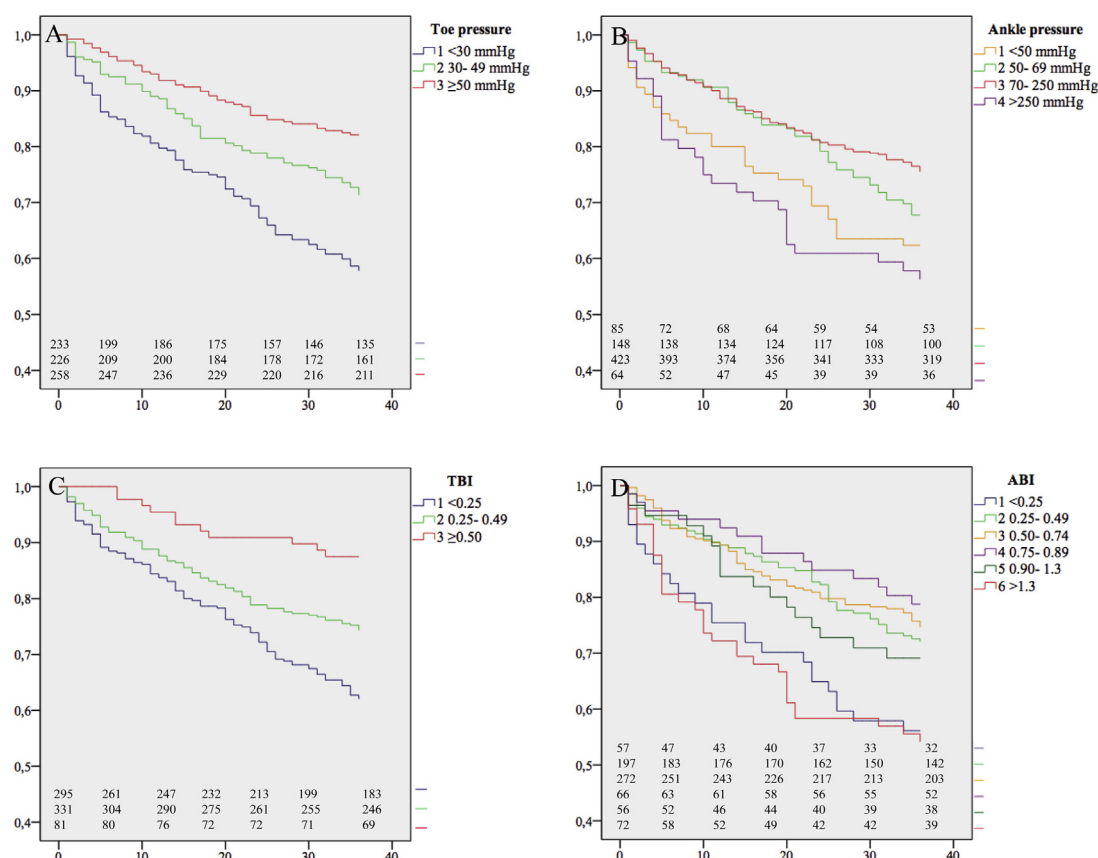
### ABI and patient outcome

Cardiovascular survival within the ABI groups was as follows: (i) ABI < 0.25: 27.5 months (SE 1.9; 95% CI 23.7–31.2); (ii) ABI 0.25–0.49: 32.9 months (SE 0.70; 95% CI



**Figure 1.** Kaplan–Meier curves demonstrating mid-term (36 month) cardiovascular mortality among the study cohort. (A) Toe pressure grouping as follows: < 30 mmHg, 30–49 mmHg, and  $\geq$  50 mmHg. (B) Ankle pressure grouping as follows: < 50 mmHg, 50–69 mmHg,  $\geq$  70 mmHg, and  $>$  250 mmHg. (C) Toe brachial index (TBI) grouping as follows: < 0.25, 0.25–0.49, and  $\geq$  0.50. (D) Ankle brachial index (ABI) grouping as follows: < 0.25, 0.25–0.49, 0.50–0.74, 0.75–0.89, 0.90–1.30, and  $>$  1.30. Lower part of figure indicates number of patients at risk entering interval at each group for 0, 6, 12, 18, 24, 30, and 36 months.





**Figure 2.** Kaplan–Meier curves demonstrating mid-term (36 month) overall mortality. (A) Toe pressure grouping as follows: < 30 mmHg, 30–49 mmHg, and > 50 mmHg. (B) Ankle pressure grouping as follows: < 50 mmHg, 50–69 mmHg, ≥ 70 mmHg, and > 250 mmHg. (C) Toe brachial index (TBI) grouping as follows: < 0.25, 0.25–0.49, and ≥ 0.50. (D) Ankle brachial index (ABI) grouping as follows: < 0.25, 0.25–0.49, 0.50–0.74, 0.75–0.89, 0.90–1.30, and > 1.30. Lower part of figure indicates number of patients at risk entering interval at each group for 0, 6, 12, 18, 24, 30, and 36 months.

31.6–34.3); (iii) ABI 0.50–0.75: 33.4 months (SE 0.58; 95% CI 32.3–34.6); (iv) ABI 0.75–0.89: 34.3 months (SE 0.97; 95% CI 32.4–36.2); (v) ABI 0.90–1.30: 31.4 months (SE 1.5; 95% CI 28.5–34.4); and (vi) ABI > 1.30: 29.3 months (SE 1.6; 95% CI 26.3–32.4). Cardiovascular deaths were most prevalent in the group of patients with an ABI < 0.25, and the difference was significant compared with the groups with an ABI 0.25–0.49 ( $p = .007$ ), 0.50–0.75 ( $p < .001$ ), and 0.75–0.89 ( $p = .004$ ) (Fig. 1D). For OS and AFS Kaplan–Meier curves are presented in Figs 2(D) and 3(D), respectively.

### Cox regression analysis

For the multivariate Cox regression analysis, risk factors were selected according to the Cox univariate analysis. For all three outcomes, age, CAD, CVD, hypertension, diabetes, ESRD, dyslipidemia, and smoking history were added to the model based on  $p < .15$ . For analysis of cardiovascular mortality, COPD was also added to the model owing to  $p < .15$ .

Including TP in multivariate analysis showed that for all study endpoints (cardiovascular and overall mortality and amputation or death) TP < 30 mmHg (vs. TP ≥ 50 mmHg) was associated with a significant risk (hazards ratio [HR]

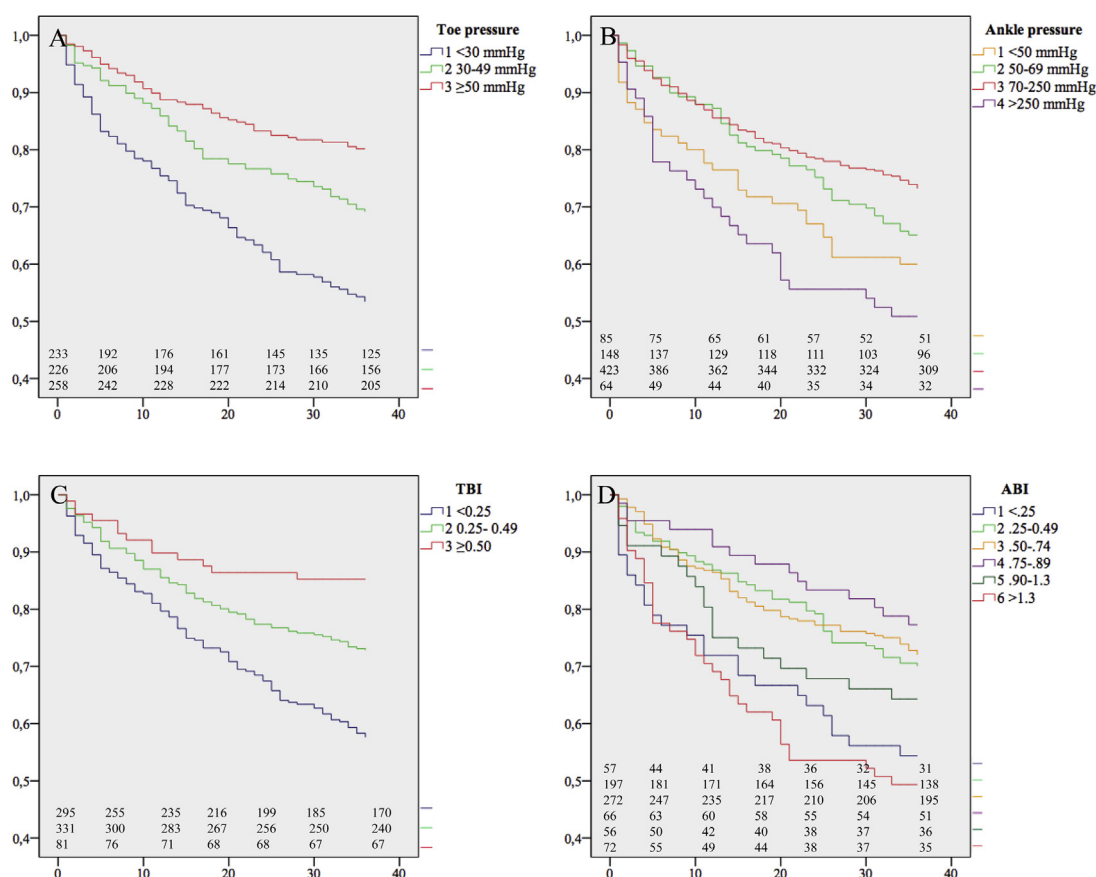
2.84, 95% CI 4.61–1.75 [ $p < .001$ ]; HR 2.05, 95% CI 2.92–1.44 [ $p < .001$ ]; HR 2.13, 95% CI 2.98–1.52 [ $p < .001$ ], respectively) (see Table 3). For all selected risk factors and study endpoints, and results of the Cox models see Tables S2–S4 (Supplementary Material).

Multivariate analysis, including TBI, showed that for all three study endpoints (cardiovascular and overall mortality and amputation or death) TBI < 0.25 (vs. TBI ≥ 0.50) was associated with a significant risk (HR 3.68, 95% CI 1.5–9.2 [ $p = .05$ ]; HR 2.53, 95% CI 1.3–4.7 [ $p = .04$ ]; HR 2.46, 95% CI 1.4–4.4 [ $p = .02$ ], respectively) (see Table 4). For all selected risk factors and study endpoints, and the results of the Cox models see Tables S2–S4 (Supplementary Material).

Multivariate analysis did not show any significant risk associations for the AP and ABI groups. For all risk factors and study endpoints, and results of the Cox models, see Tables S2–S4 (Supplementary Material).

### DISCUSSION

The association of an ABI < 0.9 with an increased rate of cardiovascular events and overall mortality has been known for decades.<sup>20,21</sup> The relationship is U-shaped owing to incompressible leg arteries affecting the values, especially among diabetics.<sup>8,9</sup> In a series of patients with PAD, with



**Figure 3.** Kaplan–Meier curves demonstrating mid-term (36 month) amputation free survival. (A) Toe pressure grouping as follows: < 30 mmHg, 30–49 mmHg, and > 50 mmHg. (B) Ankle pressure grouping as follows: < 50 mmHg, 50–69 mmHg, ≥ 70 mmHg, and > 250 mmHg. (C) Toe brachial index (TBI) grouping as follows: < 0.25, 0.25–0.49, and ≥ 0.50. (D) Ankle brachial index (ABI) grouping as follows: < 0.25, 0.25–0.49, 0.50–0.74, 0.75–0.89, 0.90–1.30, and > 1.30. Lower part of figure indicates number of patients at risk entering interval at each group for 0, 6, 12, 18, 24, 30, and 36 months.

**Table 3.** The result of multivariate analysis on the association between toe pressure (TP) and cardiovascular mortality, overall mortality, and amputation free survival (AFS).

	HR	95% CI	p
Cardiovascular mortality			
TP < 30 mmHg	2.84	1.75–4.61	< .001
TP 30–49 mmHg	1.61	0.96–2.70	.720
TP ≥ 50 mmHg	Reference		
Overall mortality			
TP < 30 mmHg	2.05	1.44–2.92	< .001
TP 30–49 mmHg	1.33	0.91–1.94	1.00
TP ≥ 50 mmHg	Reference		
AFS			
TP < 30 mmHg	2.13	1.52–2.98	< .001
TP 30–49 mmHg	1.29	0.90–1.85	1.00
TP ≥ 50 mmHg	Reference		

**Note.** The risk factors were selected for the model according to Cox univariate analysis with a *p* value < .15 as follows: age, coronary artery disease, cerebrovascular disease, diabetes, hypertension, end stage renal disease, dyslipidemia and smoking history (overall mortality and AFS), and additionally chronic obstructive pulmonary disease for cardiovascular outcome analysis. HR = hazard ratio; CI = confidence interval.

**Table 4.** Results of multivariate analysis on the association between toe brachial index (TBI) and cardiovascular mortality, overall mortality, and amputation or death.

	HR	95% CI	p
Cardiovascular mortality			
TBI < 0.25	3.68	1.48–9.19	.05
TBI 0.25–0.49	2.11	0.83–5.35	1.00
TBI ≥ 0.50	Reference		
Overall mortality			
TBI < 0.25	2.53	1.35v4.74	.04
TBI 0.25–0.49	1.94	1.03–3.64	.410
TBI ≥ 0.50	Reference		
Amputation or death			
TBI < 0.25	2.47	1.38–4.40	.050
TBI 0.25–0.49	1.70	0.94–3.05	1.00
TBI ≥ 0.50	Reference		

**Note.** The risk factors were selected for the model according to Cox univariate analysis with a *p* value < .15 as follows: age, coronary artery disease, cerebrovascular disease, diabetes, hypertension, end stage renal disease, dyslipidemia, and smoking history (overall mortality and amputation or death) and additionally chronic obstructive pulmonary disease for cardiovascular outcome analysis.

and without diabetes, an ABI  $> 1.3$  increased amputation rates in both groups in a similar fashion.<sup>22</sup> Studies on the association between TP and patient outcome are scarce. A few studies have demonstrated the predictive effect of TBI on cardiovascular mortality and morbidity, irrespective of the diabetic status of the patient.<sup>9,23</sup> In this study, which included  $> 700$  patients with TP measurements, a linear correlation between TP and TBI with cardiovascular and overall mortality, as well as AFS, was shown. Furthermore, in line with earlier studies, a U-shaped correlation between ABI and all three investigated endpoints was observed. The data emphasise the pitfalls in relying solely on ABI when assessing patients with PAD and their prognosis. In the present study population 41% were diabetic and 10% had incompressible leg arteries with an ABI  $> 1.3$ . Moreover, it is conceivable that APs in some limbs may be falsely high owing to undetected partial vessel wall incompressibility.

The role of TBI in diagnosing PAD is indefinable, and criteria for stratifying normal versus pathological TBI remain ambiguous. Guidelines recommend  $< 0.70$  as a cutoff, but this is not entirely evidence based.<sup>24</sup> There are no data confirming the utility of TBI in early detection of PAD among diabetics. In a recent Dutch study, which included patients with an ABI  $\leq 1.4$ , diabetes appeared to falsify ABI and TBI in a similar fashion.<sup>11</sup> It may be worth noting that, in the present study, 7% of patients with a TBI  $\geq 0.25$  had a TP  $< 30$  mmHg. Nonetheless, an increased cardiovascular mortality and poor OS in the group with a TBI  $< 0.25$  was observed. Between the defined categories, the increased risk was step wise. This result is in line with a previous study by Hyun *et al.*,<sup>9</sup> although their approach was different. A normal TBI value was a rarity in the present study, with the indices of only eight patients exceeding 0.75.

The risk of amputation has been demonstrated to be associated with low TP values.<sup>25–27</sup> According to the present data, TP has a strong association with mid-term cardiovascular and all-cause mortality, as well as AFS. All-cause mortality has previously been linked to low TP in a relatively small cohort of 53 patients and 76 limbs, with similar results to the data presented here.<sup>26</sup> The current study is an analysis of 732 patients. TP values fulfilling the criteria for CLI were observed in 233 patients (TP  $< 30$  mmHg). The findings further support the notion that TP may serve as a powerful, non-invasive tool for detecting patients at highest risk of death and therefore being in need of optimal medical prevention of major cardiovascular events, death, or major amputation. The use of TP as a single prognostic or diagnostic tool for the evaluation of patients at risk of cardiovascular events is a tempting option, as it is a simple, non-invasive method available even in a general practitioner's office.<sup>24</sup> It may also provide a tool superior to ABI for screening high risk patients at diabetes outpatient clinics, owing to linear risk stratification.

In the present study, TP measurements were categorized according to criteria for CLI.<sup>16,17,28</sup> It is generally accepted that CLI is associated with poor patient outcome.<sup>20,29</sup> According to the present data, a TP  $< 50$  mmHg, and especially a TP  $< 30$  mmHg, is significantly associated with poor

patient outcome, further supporting the malignant nature of CLI.

Poor exercise capacity has been suggested to be the strongest predictor of mortality among patients with PAD, even compared with all earlier known major risk factors for PAD and CAD.<sup>30,31</sup> Non-invasive limb pressure measurements were not assessed by these analyses. The prognostic value of combined exercise capacity and distal non-invasive pressure measurements on mortality is a tempting target for further studies.

When considering generalisation of the present results, it should be kept in mind that all the patients had symptomatic PAD and were referred for DSA by a vascular specialist. Thus, the cohort did not include individuals who did not fulfill the criteria for invasive treatment and are preferentially taken care of by primary healthcare. However, the study population was wide and heterogeneous, as it contained patients irrespective of diabetic status or PAD history. Owing to this, the results obtained should be widely applicable to everyday vascular practice.

## CONCLUSIONS

Earlier studies have also demonstrated a U-shaped prognostic value of ABI on patient survival. In addition, ABI has been shown to be a potent non-invasive tool in PAD screening. In many vascular units, AP, ABI, TP, and TBI are essential measurements for clinical decision making and are routinely analysed in everyday practice. There are no earlier studies comparing all four variables and patient outcome in a single study setting. Based on the present observations, it is suggested that non-invasive measurement of TP and TBI are predictive of cardiovascular mortality, overall mortality, and AFS in patients with PAD, in a linear fashion.

## CONFLICTS OF INTEREST

None.

## FUNDING

This study was supported by a grant from South-Western Finland Cultural Foundation, Hertta and Veikko Valtonen trust fund, and an EVO grant, Turku University Hospital.

## APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejvs.2017.02.012>.

## REFERENCES

- Mendis S, Lindholm LH, Anderson SG, Alwan A, Koju R, Onwubere BJC, et al. Total cardiovascular risk approach to improve efficiency of cardiovascular prevention in resource constrain settings. *J Clin Epidemiol* 2011;**64**(12):1451–62.
- Lin JS, Olson CM, Johnson ES, Whitlock EP. The ankle-brachial index for peripheral artery disease screening and cardiovascular disease prediction among asymptomatic adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013;**159**(5):333–41.



- 3 Fowkes FGR, Murray GD, Butcher I, Folsom AR, Hirsch AT, Couper DJ, et al. Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events. *Eur J Prev Cardiol* 2014;**21**(3):310–20.
- 4 Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol* 1999;**19**(3):538–45.
- 5 Wild SH, Byrne CD, Smith FB, Lee AJ, Fowkes FGR. Low ankle-brachial pressure index predicts increased risk of cardiovascular disease independent of the metabolic syndrome and conventional cardiovascular risk factors in the Edinburgh Artery Study. *Diabetes Care* 2006;**29**(3):637–42.
- 6 Leskinen Y, Salenius JP, Lehtimäki T, Huhtala H, Saha H. The prevalence of peripheral arterial disease and medial arterial calcification in patients with chronic renal failure: requirements for diagnostics. *Am J Kidney Dis* 2002;**40**(3):472–9.
- 7 Potier L, Halbron M, Bouilloud F, Dadon M, Le Doeuff J, Ha Van G, et al. Ankle-to-brachial ratio index underestimates the prevalence of peripheral occlusive disease in diabetic patients at high risk for arterial disease. *Diabetes Care* 2009;**32**(4):e44.
- 8 Suominen V, Uurto I, Saarinen J, Venermo M, Salenius J. PAD as a risk factor for mortality among patients with elevated ABI—a clinical study. *Eur J Vasc Endovasc Surg* 2010;**39**(3):316–22.
- 9 Hyun S, Forbang NI, Allison MA, Denenberg JO, Criqui MH, Ix JH. Ankle-brachial index, toe-brachial index, and cardiovascular mortality in persons with and without diabetes mellitus. *J Vasc Surg* 2014;**60**(2):390–5.
- 10 Høyer C, Sandermann J, Petersen LJ. The toe-brachial index in the diagnosis of peripheral arterial disease. *J Vasc Surg* 2013;**58**(1):231–8.
- 11 Stoekenbroek RM, Ubbink DT, Reekers JA, Koolemay MJW. Hide and seek: does the toe-brachial index allow for earlier recognition of peripheral arterial disease in diabetic patients? *Eur J Vasc Endovasc Surg* 2015;**49**(2):192–8.
- 12 Marston WA, Davies SW, Armstrong B, Farber MA, Mendes RC, Fulton JJ, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. *J Vasc Surg* 2006;**44**(1):108–14.
- 13 Vallabhaneni R, Kalbaugh CA, Kouri A, Farber MA, Marston WA. Current accepted hemodynamic criteria for critical limb ischemia do not accurately stratify patients at high risk for limb loss. *J Vasc Surg* 2016;**63**(1):105–12.
- 14 Carter SA, Tate RB. The value of toe pulse waves in determination of risks for limb amputation and death in patients with peripheral arterial disease and skin ulcers or gangrene. *J Vasc Surg* 2001;**33**(4):708–14.
- 15 Norgren L, Hiatt WR, Harris KA, Lammer J. TASC II Working Group. TASC II section F on revascularization in PAD. *J Endovasc Ther* 2007;**14**(5):743–4.
- 16 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;**45**(Suppl. S):S5–67.
- 17 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;**33**(1):S1–75.
- 18 Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIFI). *J Vasc Surg* 2014. 220–34.e1–2.
- 19 Mehler PS, Coll JR, Estacio R, Esler A, Schrier RW, Hiatt WR. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. *Circulation* 2003;**107**(5):753–6.
- 20 Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;**326**(6):381–6.
- 21 Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**(2):197–208.
- 22 Silvestro A, Diehm N, Savolainen H, Do D-D, Vögele J, Mahler F, et al. Falsely high ankle-brachial index predicts major amputation in critical limb ischemia. *Vasc Med* 2006;**11**(2):69–74.
- 23 Martín-Fuentes M, Herranz L, Saez-de-Ibarra L, Pallardo LF. Low toe-brachial pressure index predicts increased risk of recurrent cardiovascular disease in type 2 diabetes. *Diabetes Care* 2015;**38**(4):e53–4.
- 24 Høyer C, Sandermann J, Petersen LJ. Randomised diagnostic accuracy study of a fully automated portable device for diagnosing peripheral arterial disease by measuring the toe-brachial index. *Eur J Vasc Endovasc Surg* 2013;**45**(1):57–64.
- 25 Nielsen PH, Andersen HJ, Bille S, Holstein P, Egeblad K. The ischaemic leg: a long-term follow-up with special reference to the predictive value of the systolic digital blood pressure. Part II: After arterial reconstruction. *Thorac Cardiovasc Surg* 1989;**37**(6):351–4.
- 26 Andersen HJ, Nielsen PH, Bille S, Holstein P, Egeblad K. The ischaemic leg: a long-term follow-up with special reference to the predictive value of the systolic digital blood pressure. Part I: No arterial reconstruction. *Thorac Cardiovasc Surg* 1989;**37**(6):348–50.
- 27 Varatharajan N, Pillay S, Hitos K, Fletcher JP. Implications of low great toe pressures in clinical practice. *ANZ J Surg* 2006;**76**(4):218–21.
- 28 Olin JW, Allie DE, Belkin M, Bonow RO, Casey DE, Creager MA, et al. ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease. *J Vasc Surg* 2010;**52**(6):1616–52.
- 29 Shiraki T, Iida O, Takahara M, Okamoto S, Kitano I, Tsuji Y, et al. Predictive scoring model of mortality after surgical or endovascular revascularization in patients with critical limb ischemia. *J Vasc Surg* 2014;**60**(2):383–9.
- 30 Leeper NJ, Myers J, Zhou M, Nead KT, Syed A, Kojima Y, et al. Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease. *J Vasc Surg* 2013;**57**(3):728–33.
- 31 Myers J, Nead KT, Chang P, Abella J, Kokkinos P, Leeper NJ. Improved reclassification of mortality risk by assessment of physical activity in patients referred for exercise testing. *Am J Med* 2015;**128**(4):396–402.